APPENDIX VII

SMOKER INTAKE FROM CIGARETTES IN THE 1 MG TAR CLASS

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Smoker Intake from Cigarettes in the 1 mg Tar Class

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ABSTRACT

In the U.S., cigarette yields are measured according to standard analytical procedures issued by the Federal Trade Commission (FTC). Concern has been raised that such measurements may not be sufficiently informative to consumers of low yield cigarettes, whose smoke intake may depend mainly on the aggressiveness of personal behavior and cigarette characteristics other than yield. This study determined relative smoke intake in smokers of cigarettes in the 1 mg tar class who switched brands. Intake was measured as plasma levels of cotinine, a direct metabolite and good indicator of nicotine intake. All brands tested resulted in cotinine levels over a similar range of values from non-detectable to some 900 ng/ml. However, the overall mean levels for each brand, as well as the brand differences in individual smokers, were closely proportional to the small analytical differences of FTC

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nicotine yields for each brand smoked. The implication is that FTC values may not predict the absolute intake of individual smokers, a task they could not be asked to achieve; however, they appear to offer valid information about the relative intake that individual smokers may expect from different brands in the 1 mg tar class.

INTRODUCTION

Numerous studies of cigarette smoking indicate that the intensity of effects depends on the dose inhaled (1). On this basis, cigarettes of low smoke yield have been advocated as being less hazardous. Considerable epidemiologic and laboratory evidence supports this advice (2), although controversy has risen over the definition and ranking of less hazardous cigarettes.

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In the United States cigarette yields are officially measured using a standardized analytical procedure adopted many years ago by the Federal Trade Commission (FTC) with wide concurrence (3). Similar methods are used in other countries. Lately, concerns over the differences of individual smoking behavior have questioned whether the standardization of the FTC methodology is relevant in providing the consumer with a ranking of commercial cigarettes (4, 5, 6, 7). The particular implication has been that intake variance may be more pronounced for smokers of low yield cigarettes, where it may be affected by cigarette characteristics other than tar and nicotine yields, e.g. resistance to draw, etc.

The problem of measuring natural intake during field smoking conditions is complicated by the imposition of any experimental schedule, especially when smokers are asked to switch brands of substantially

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different yields. Here, their immediate behavioral changes are determined by a mixture of organoleptic (e.g. flavor), pharmacologic (e.g. nicotine), kinesthetic (e.g. draw resistance), and psychological (e.g. novelty), factors, some of which subside after some time, while others remain to define permanent adjustments to the new cigarettes. The time to reach a new equilibrium varies with individuals, but it is probably in the order of weeks (5, 8, 9). Because of this, experiments focusing on the immediate outcome of switching to and from brands of markedly different yields are unlikely to inform about those stabilized conditions that eventually take over.

The present study set forth to measure the range of smoke intake in individual smokers of three popular U.S. cigarette brands, advertised as nominally yielding 1 mg of tar by the FTC method. It also addresses the question of how smokers respond to small differences in FTC smoke yields, as they switch from one to another of these brands.

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Testing these questions with smokers of cigarettes of the same FTC yield class, is likely to avoid significant distortions of compensatory behavior, and justifies an experiment of relatively short duration (9).

Evidence for compensation has been obtained by measuring the number of cigarettes smoked, extent of tampering with filtration and smoke dilution devices, or the observation of greater volume and frequency of puffs and inhalation (4, 5, 6, 7). Clearly, these inferential measures do not provide a direct indication of smoke intake.

At the present state-of-the-art, cigarette smoke intake in man can be measured directly only through suitable markers in the blood of smokers, thus bypassing the uncertainties of indirect assessments. Carbon monoxide (CO), nicotine, and cotinine have been utilized for this purpose. The first has been questioned because smokers are exposed to CO from automobile emissions and other domestic,

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occupational and industrial sources. Also, CO could originate from endogenous physiologic processes (10). Correlations of expired CO and plasma nicotine values have been found in well controlled and limited experiments conducted in restricted laboratory settings, utilizing few subjects and cigarettes of relatively high CO yields (11). However, the confounding influence of exogenous sources can be expected to be severe when large numbers of users of low CO cigarettes are asked to smoke under free ranging conditions, as in the present study.

Nicotine is obviously a most specific marker of tobacco smoke, although it is present in insignificant amounts in tomatoes, peppers and eggplant. While measurements vary, an approximation of its terminal half life is some 40 - 100 minutes in the bloodstream. This is likely to make its determination sensitive to short-time sampling variables, and to reflect mainly the input from the last two or three cigarettes smoked (12, 13, 14, 16). Its excretion rate also depends partially on

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urine pH, resorption and other transient factors (17, 18, 21, 22), although these can be expected to contribute negligibly to variance if blood sampling is close to the actual time of cigarette smoking.

Potentially, a more serious difficulty in using nicotine as a marker is that individuals smoke with different intensity at different times of the day, when satiation sets in, or under stress as, for instance, during an experimental blood sampling session. The ideal marker would give an average indication of the cumulative results of discrete intake episodes over a suitable period of time, and should not represent simply the momentary experience of smoking one or two cigarettes.

Several human and animal studies have shown cotinine to be a principal and direct metabolite of nicotine, from which it arises at predictable and defined rates (13, 14, 15, 16). This correspondence is confirmed by the good linear correlation of nicotine and nicotine plasma levels,

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as reported later in this study and by others (14). A terminal half-life of some 20 - 30 hours makes cotinine insensitive to short-time sampling variables, and requires only that subjects be sampled during late afternoon and at fixed days during the week, to equalize weekly and circadian steady-state patterns (14). On this account, cotinine is probably a better indicator of overall cumulative intake during undisturbed smoking activities, not significantly affected by immediate experimental stress behavior as nicotine intake could be. It is also present in plasma at concentrations 10 fold higher than nicotine, and demands less strict analytical procedures.

It should be noted that the kinetics of nicotine excretion and metabolism are poorly understood. Variations in individual behavior, weight, lean body mass and urinary pH will result in a range of plasma nicotine and cotinine values in different individuals smoking the same cigarettes (12-18, 20, 21). The metabolism of nicotine in the liver,

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its major site of detoxification, is mediated by microsomal enzymes that can be activated or depressed by a number of dietary components, alcohol, drugs, pathologic and physiologic conditions (12-16). Such reasons and others preclude reliable quantitative estimates of smoke intake from plasma nicotine and cotinine levels. Nevertheless, these sources of variance are clearly not sufficient to unduly affect the observed linear correlation of plasma nicotine and cotinine levels, nor the week by week stability of cotinine levels in the subjects of our study. This suggests that, while metabolic and excretion dynamics may be different among individuals, they are likely to remain more stationary in the same individual over a relatively short time when diet, health status, medication and stress conditions remain virtually unchanged. Thus it is reasonable to conclude that changes in the plasma nicotine and cotinine of individual smokers, switching from brand to similar brand over a controlled time span, represent their individual experience with each brand, and give a reliable indication of their relative intake from each brand.

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Therefore, the experiment was designed so that it could also be analyzed as a sequential one, considering individual smokers as they switch brands. In this self-matching analysis, individual smokers provide their own control, and the ratios of cotinine levels generated by each brand give a measure of the relative position of that brand.

Significantly, nicotine is delivered in close physical association with tar particles (19). Only a negligible amount is delivered in the vapor phase, and at the average pH of cigarette smoke most of it is absorbed in the lungs and not in the upper respiratory tract (20). Upon contact with the lung surface nicotine is rapidly transferred to the bloodstream, while less soluble tar components are first absorbed on the surface. Because of this, nicotine and cotinine are also valid indicators of tar intake, once the ratio of tar to nicotine of a cigarette's smoke is known.

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As a working hypothesis, we adopted the proposition that nicotine may be proportional to the FTC nicotine delivery of the cigarette smoked. Thus, plasma levels of cotinine would also be proportional to nicotine intake, to FTC nicotine yields and, by suitable transformation to FTC tar yields.

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MATERIALS AND METHODS

Cigarettes

The study utilized three commercial brands (A, B and C) belonging to the 1 mg FTC tar class. All cigarettes were purchased from commercial distributors, each brand coming from the same production batch, to minimize input variance. Specific analytical data are summarized in Table 1.

Subjects

Behavioral distortions could bias the hypothesis testing, especially compensatory up-shifts that could be expected if the subjects had been habitually smoking high yield cigarettes (22, 23, 24, 25.) Therefore, the study was designed so that participants would continue to smoke as

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closely as possible to their habitual practices. Subjects were selected who customarily smoked either A or B Brand cigarettes yielding 1 mg nominal FTC tar. They were allowed to smoke under natural free conditions, as contrasted to an artificial or quasi-controlled experimental setting. The subjects (288 smokers, 117 men and 171 women) were approached randomly in shopping malls and through notices in community newspapers in each of five cities. Accepted respondents were at least 21 years of age, had been smoking at least 20 cigarettes daily for at least three months, and engaged in no other smoking-related practices (cigars, pipes, snuff, chewing tobacco, nontobacco smoking products). Only individuals in good health under no medication were recruited. Subjects were dropped from the study if disease and medical treatment intervened. Individuals with obvious alcoholic problems were also excluded. Each subject was informed at the outset that participation in the study would require smoking specific 1 mg tar brands provided free of charge; they also were asked not to change consciously any of their customary smoking practices.

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Schedule

On their first visit, the subjects completed a brief questionnaire on their smoking history and related factors, and provided a 10 ml sample of venous blood for baseline cotinine analysis. Subjects were sampled in late afternoon on Wednesdays or Thursdays, in order to equalize circadian and weekly behavioral patterns and pharmacodynamic conditions.

Each respondent was given a week's supply of his/her own customary brand of cigarettes to smoke for the following week, and a cigarette tally sheet to record the exact time for each cigarette smoked in the 48 hours preceeding sampling. They were also provided with special containers, to collect all butts of the cigarettes smoked during the tallying period. Respondents reported on the following week and provided venous blood samples, as before. These data comprised a second set of baseline values.

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At this point smokers of Brand A were given Brand B and vice versa. Respondents stayed on the alternate brand for three weeks, reporting to the test center weekly to provide venous blood, to obtain additional supplies of cigarettes, and to turn in the completed cigarette tally sheets.

Starting with the fifth visit to one of the test centers, all respondents were given Brand C cigarettes to smoke for two weeks, once again reporting to the center each week for blood samples. The sequence of brands smoked is summarized in Table 2. All subjects received a nominal monetary compensation at each sampling.

Nicotine - Cotinine Correlation

A separate group of 45 male and 41 female smokers of 1 mg tar cigarettes (31 Brand A, 35 Brand B, 15 Brand C, 5 Brand D) was recruited for the purpose of validating plasma cotinine as a marker of

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plasma nicotine and smoke intake. These subjects had general characteristics as for the main group above, but special precautions were taken to insure that daily steady-state conditions for plasma nicotine and cotinine were well standardized, as required by pharmacokinetic considerations and previous experiences (14). To this end, the subjects in this group habitually smoked at regular intervals during the day, and especially during the three hours preceeding the sampling. Blood withdrawal for this group occured at the first time the subjects presented themselves, and was performed usually on a Thursday betweem 5:00 and 7:00 pm. These precautions are absolutely necessary for a realistic correlation. Sampling indiscriminately during the week would give results that are distorted by the behavioral changes that most smokers experience on weekends. Morning sampling, on the other hand, will also distort the correlation, because of the different times required to reach peak steady-state levels of plasma nicotine and cotinine (14). A control group of 23 male and 26 female nonsmokers was also recruited and sampled for plasma nicotine and cotinine.

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Blood Samples

Blood samples were drawn by a certified technician; plasma was obtained by centrifugation and frozen without preservatives within fifteen minutes of being drawn. Samples were blind coded, shipped and stored frozen at -20°C or below.

Cotinine and Nicotine Analysis

Cotinine and nicotine levels in plasma were determined using methods developed by Jacob et al. (25). Standard curves were constructed and repeated every 40 determinations, by adding internal standards (N-ethylnornicotine for nicotine, and N-(2 Methoxyethyl) norcotinine for cotinine) to blank plasma samples which were carried through the extraction procedure. The peak height correlation was linear over the

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range 0 to 600 ng/ml for cotinine, and 0 - 100 ng/ml for nicotine. Throughout the procedure, precautions were taken to avoid exogenous contamination (27).

As a quality control check, 178 plasma samples were selected randomly for re-analysis of cotinine values. The average of the original values was 245 ng/ml, with SEM of 11.4 ng/ml. The duplicate values had an average of 258 ng/ml, with SEM of 11.9 ng/ml. The linear correlation coefficient between the original and duplicate values was 0.93, and the paired t-test was not significant at P = 0.05. For nicotine, 21 samples were selected at random for re-analysis. The average of the original values was 26.3 with SEM 2.5 ng/ml; the duplicate set had an average of 26.8 with SEM 2.3 ng/ml. The paired t-test value was not significant at P = 0.05. These statistics suggest a high level of consistency in the analytical methodology.

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To exclude possible interferences from other compounds in the analysis of cotinine and nicotine, a random group of samples was analyzed by high resolution gas chromatography and mass spectrometry (GS/MS). Ten plasma samples, previously analyzed as above, were processed according to our analytical methodology for the determination of cotinine. Prior to GC/MS analysis the sample extracts were pooled and concentrated to a volume of 20 ul. A 1 ul aliquot was then analyzed by GC/MS. The GC/MS conditions were:

GC/MS: Finnagan 4000
AMU Range: 35-450
Scan Speed: 1 scan per second
Mode: Electron Impact
Column: Fused silica, 30M x 0.312 mm
Flow Rate: 2 ml/min
Liquid Phase: DB5, J & W Scientific
Temperature Program: 50°C (4 min) to 280°C at 8°C/min
Injector Temperature: 260°C
Injection Volume: 1 ul, splitless

No interfering molecules were found. The calculated concentration of cotinine was 594 ng/ml by GC/MS, comparing favorably with the 526 ng/ml measured by the GC analysis routinely used.

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RESULTS

Subject characterisitcs

General characteristics of the subjects entering the study are summarized in Table 3 and Figures 1 and 2. The groups represented predominantly white collar occupations and housewives. Male - female differences are reflected throughout the results, thus requiring separate analysis of the data.

Plasma Cotinine

Mean values of plasma cotinine measurements are summarized in Table 4, broken out by the brand of cigarettes customarily smoked, by sex, and stratified into three baseline range levels in order to compare smokers

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with similar intake habits and demand. Baseline values were averaged over the first two measurements taken, while each respondent had been smoking his/her customary brand. The alternate brand values are averaged over the separate measurements for each respondent, when Brand A smokers were smoking Brand B and viceversa (see table 1). The last set of values in Table 4 are averages over the two weekly spans when all respondents were smoking Brand C.

Table 5, summarizes the mean values and associated standard errors of the plasma cotinine measurements broken out by groups having homogeneous characteristics, i.e. by the brand of cigarettes customarily smoked, and by sex. Overall baseline values were averaged over the first two measurements taken, while each respondent had been smoking his/her customary brand. The overall alternate brand values are averaged over three separate measurements for each respondent. The last set of values in Table 5 gives overall averages over the two time

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periods when all respondents were smoking Brand C. No statistically significant differences (P = 0.05) were noted between observed and expected values in a self-matching paired t test analysis, except in the two instances given in Table 5. Although significant, these two deviations are very small and do not affect the overall conclusion, namely that for the low yield cigarettes tested, individual smoker plasma cotinine levels and intake of nicotine are closely proportional to the small differences of nicotine yields among brands, as determined by FTC methods (Figure 3 and Table 5). Expected values were made to reflect the FTC nicotine yield ratios for the brands smoked (Table 1).

In a consolidated assessment, Table 6 summarizes the results for all respondents as they smoked the three brands tested. Because the level of cotinine partially depends on the number of cigarettes smoked daily, (figure 4), a normalization was carried out for each data point of each respondent, by dividing his/her plasma cotinine values by the number of

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daily cigarettes used prior to that sampling. Averages of these normalized values are given in Table 6. The ratios of these averages agreed well with the ratios of the analytical nicotine yields of the cigarettes tested (Table 2). Maximum recorded values of plasma cotinine are also given in Table 6, indicating that each brand tested is capable of generating a similar range of values.

The sample coefficient of skewness was calculated for each experimental set of values. In all cases the coefficient was positive, suggesting a slight dispersion of values to the right of the mean. No coefficient was significantly greater than zero ($P = 0.05$), nor did any coefficient change significantly for any group, indicating that the mean values given in Tables 4, 5, and 6 are free of distortion from dispersed sample points.

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Number of cigarettes smoked daily

As calculated from the respondent's tally sheets, Table 7 summarizes the average numbers of cigarettes smoked daily, broken out by the brand customarily smoked, and by sex.

In all four groups of respondents, the least number of cigarettes smoked was for Brand A. The men smoked the largest numbers of cigarettes while on Brand C and the women smoked the largest number of cigarettes while on Brand B. The average change was always below 10%. Paired t-tests for each individual experience, revealed no significant differences at P = 0.05, suggesting negligible compensation in the number of cigarettes smoked daily.

Figure 4 shows that baseline plasma cotinine levels are positively correlated with the number of cigarettes smoked daily.

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Nicotine-Cotinine Correlation

Figure 5 gives all data from a group of 86 male and female subjects expressly sampled to explore the correlation of plasma nicotine and cotinine. The linear correlation coefficient $r = 0.84$ is significant at $P = 0.001$. In the control group of nonsmokers, no subject had a detectable level of plasma cotinine (25 ng/ml or greater). Plasma nicotine in the males ranged from 0.5 to 4.8 ng/ml, with a mean value of 1.9 ng/ml and a S.E.M. of 0.3 ng/ml. For the females, the plasma nicotine ranged from non-detectable to 7.7 ng/ml, with a mean value of 1.5 ng/ml and S.E.M. of 0.3 ng/ml. The male and female subjects combined had an average plasma nicotine level of 1.7 ng/ml, with a S.E.M. of 0.3 ng/ml. The correlation in Figure 5 does not include values for the nonsmoking controls.

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Plasma Cotinine and Daily Available Nicotine

Figures 6 and 7 give male and female data relating baseline plasma cotinine to available daily nicotine (ADN), defined by the FTC nicotine yield of the cigarette smoked (FTC(N)), and the number (CPD) of cigarettes smoked daily: ADN = FTC(N) X CPD. A positive correlation is discernible, although - as expected - the variance is large, with $r = 0.48$ for males and $r = 0.47$ for females, both correlation coefficients being significantly greater than zero at $P \geq 0.01$. The correlation coefficients did not improve after adjusting cotinine values for subject weight indicating that behavioral and sampling factors are the more likely sources of variance, metabolic factors being probably stable on account of the good correlation of plasma nicotine and cotinine.

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CONCLUSIONS

At present there is scant knowledge of the average pharmacodynamic parameters of nicotine to cotinine transformation, excretion and metabolism. However, two observations suggest that these parameters are relatively uniform and stable in our sample of comparable subjects, and at least within the range of plasma concentrations measured. One is the correlation of plasma levels of nicotine and cotinine (Figure 5), which must be considered exceptionally good in view of the many possible sources of variance. The other is the remarkable stability of individual plasma cotinine values week after week, while smoking the same cigarette. Thus, it may not be realistic to infer precise quantitative estimates of smoke intake from plasma cotinine levels, but they are valid estimates of relative intakes from the cigarettes tested in this study.

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The validity of results is reinforced by the positive correlation and dose response between plasma cotinine levels (intake) and the daily quantity of available nicotine (smoke), as defined by the specific yield and the number of daily cigarettes smoked.

It is clear that any of the brands tested results in plasma cotinine levels over a similar range of values, depending on the behavior, metabolic and somatic characteristics of smokers. The virtually unchanging quantity of daily cigarettes smoked suggest that the same statement is valid for nicotine intake. In turn, the physical association of nicotine and tar in cigarette smoke, and the nearly equal tar to nicotine ratio of the brands tested, suggest that similar conclusions are probably valid for tar intake.

Previous studies found that compensation, at least under experimental conditions, is usually only partial (5, 9, 24, 25). In this study, and

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for the nominal 1 mg FTC tar cigarettes tested, small absolute differences in analytical cigarette yield did not elicit significant compensatory shifts, and smokers displayed plasma cotinine levels proportional to the differences of FTC nicotine yields of the brands smoked (figure 4). For individual smokers this proportionality occurs within a limited segment of the overall range of observed values, high inhalers remaining high, and vice versa. This is likely to reflect consistent individual differences in the nicotine and smoke intake requirements (Table 4). The differences observed upon switching also suggest that individual smokers of 1 mg tar cigarettes may find satiation at different levels within their personal range of nicotine and smoke intake.

In conclusion, the weight of the observations in this study suggests that, although FTC values may be inadequate quantitative indicators of actual smoke intake, they appear to be a valid representation of the relative intake that individual smokers can expect from the 1 mg FTC tar class cigarettes tested, and probably from similar brands in that class.

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Table 1. Analytical Data of Cigarettes Tested

Milligrams Per Cigarette* and Standard Deviation

Brand	Batch Code	Tar	Nicotine
A	1XL	0.9 ± 0.2	0.18 ± 0.02
B	00025	0.5 ± 0.2	0.10 ± 0.02
C	EB	0.6 ± 0.2	0.11 ± 0.02

*All Cigarettes 85 mm length, filter, soft pack.

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Table 2. Brand Smoking Schedule

	Week						
	1*	2*	3	4	5	6	7
	A	A	B	B	B	C	C
	B	B	A	A	A	C	C

*Respondents's customary brand. The sequence is in one week intervals.

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Table 3. Respondent Characteristics at First Entry

Customary Brand of cigarette	Number of respondents		Average # of mos. smoking cust. brand		Avg. # of cigarettes smoked/day		Average Age	
	M	F	M	F	M	F	M	F
Brand A	67	75	6.4	7.4	30.6	29.9	35.3	38.0
Brand B	50	96	11.8	11.6	30.2	28.0	39.8	39.1

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Table 4. Plasma Cotinine, ng/ml, Averages and (S.E.M.)

Customary Brand	Sex	Baseline Range	N	Brand A	Brand B	Brand C
Brand A	M		67	317 (8)	222 (11)	235 (17)
		< 225	20	150 (13)	130 (16)	124 (14)
		225-450	35	334 (11)	229 (16)	265 (26)
		> 450	12	544 (17)	348 (30)	327 (49)
Brand B	M		50	322 (16)	206 (9)	223 (19)
		< 225	29	242 (23)	123 (13)	151 (17)
		225-450	20	458 (18)	313 (13)	353 (43)
		> 450	1	535 (NA)	480 (NA)	327 (NA)
Brand A	F		75	328 (7)	207 (15)	203 (13)
		< 225	22	141 (14)	71 (10)	94 (16)
		225-450	37	344 (10)	223 (24)	244 (20)
		> 450	16	544 (17)	361 (38)	271 (33)
Brand B	F		96	284 (14)	189 (6)	185 (11)
		< 225	63	226 (17)	128 (8)	151 (13)
		225-450	31	399 (22)	297 (10)	253 (23)
		> 450	2	477 (NA)	460 (NA)	411 (NA)

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Table 5. Plasma Cotinine, ng/ml. Averages and (S.E.M.)

	Customary Brand A		Customary Brand B	
Sex	M	F	M	F
Initial Subjects	67	75	50	96
Baseline Entry	334	312	228	201
Baseline First Week	308	333	176	178
Baseline Overall	317 (13.9)	328 (18.0)	206 (16.8)	189 (10.9)
Alternate Brand* First Week	209	207	305	291
Alternate Brand* Second Week	235	210	342	266
Alternate Brand* Third Week	228	201	320	273
Alternate Brand*, Overall	222 (13.9)	207 (18.5)	322 (24.5)	284** (15.4)
Brand C First Week	240	212	202	192
Brand C Second Week	230	197	238	179
Brand C Overall	235 (17.3)	203 (14.0)	223 (20.2)	185*** (11.6)

*Brand A for Brand B smokers and vice versa.

**Significantly lower than expected, $P \geq 0.05$.

***Significantly lower than expected, $P \geq 0.01$.

Note. Statistical significance was determined on a self-matching basis, paired t-tests (two tailed), after adjusting individual values for the number of daily cigarettes consumed.

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Table 6. Plasma Cotinine Summary Results (S.E.M.)

Cigarette Smoked	Brand A	Brand B	Brand C
Average plasma cotinine, ng/ml	310 (10.1)	204 (8.2)	208 (8.2)
Maximum value recorded ng/ml	833	859	899
Average cigarettes smoked daily	29.0	30.5	31.1
Average Normalized Plasma Cotinine, ng/ml*	10.8	6.8	6.7
Ratio to Brand C**	0.16	0.10	0.10
Nicotine mg/cigarette	0.18	0.11	0.10

*For each respondent, plasma cotinine values were divided by his/her average daily cigarette consumption. Averages of overall results are reported.

**Ratios of the normalized plasma cotinine values taking the Brand C value as 0.10.

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Table 7. Daily Cigarette Consumption, Units, Averages and (S.E.M.)

Customary Brand	Sex	Baseline Range	N	Brand A	Brand B	Brand C
Brand A	M	20-52	67	31 (0.4)	33 (0.7)	34 (0.7)
		< 25	14	21 (0.7)	22 (0.8)	25 (1.2)
		25-35	32	30 (0.5)	33 (0.9)	34 (1.3)
		>35	21	39 (0.8)	41 (1.5)	40 (1.2)
Brand B	M	20-51	50	30 (0.8)	31 (0.4)	33 (1.1)
		< 25	13	20 (0.6)	21 (0.4)	23 (2.0)
		25-35	17	28 (1.1)	28 (0.6)	29 (1.8)
		>35	20	39 (1.8)	40 (0.8)	43 (2.0)
Brand A	F	20-55	75	29 (0.3)	31 (0.6)	30 (0.8)
		< 25	23	21 (0.4)	22 (1.2)	22 (1.3)
		25-35	35	30 (0.4)	32 (0.9)	32 (1.3)
		>35	17	39 (0.9)	41 (1.3)	41 (1.7)
Brand B	F	20-47	96	27 (0.5)	28 (0.2)	29 (0.6)
		< 25	36	20 (0.7)	20 (0.4)	21 (0.9)
		25-35	42	29 (0.8)	30 (0.4)	31 (0.8)
		>35	18	38 (1.5)	38 (0.2)	40 (2.4)

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FIGURES

Figure 1. Subject distribution according to daily cigarettes smoked at time of entry.

Figure 2. Subject distribution according to baseline plasma cotinine values.

Figure 3. Baseline plasma cotinine values as a function of FTC nicotine delivery of Brands A and B.

Figure 4. Baseline plasma cotinine as a functon of daily cigarettes smoked. Brand A and Brand B smokers.

Figure 5. Plasma cotinine values as a function of plasma nicotine values Males and Females.

Figure 6. Baseline plasma cotinine as a function of available daily nicotine (mg), defined as FTC nicotine/cigarette, multiplied by the cigarettes smoked per day. ADN = FTC (N) X CPD - Males.

Figure 7. Baseline plasma cotinine as a function of available daily nicotine (mg), defined as FTC nicotine/cigarette, multiplied by the cigarettes smoked per day. ADN = FTC (N) X CPD - Females.

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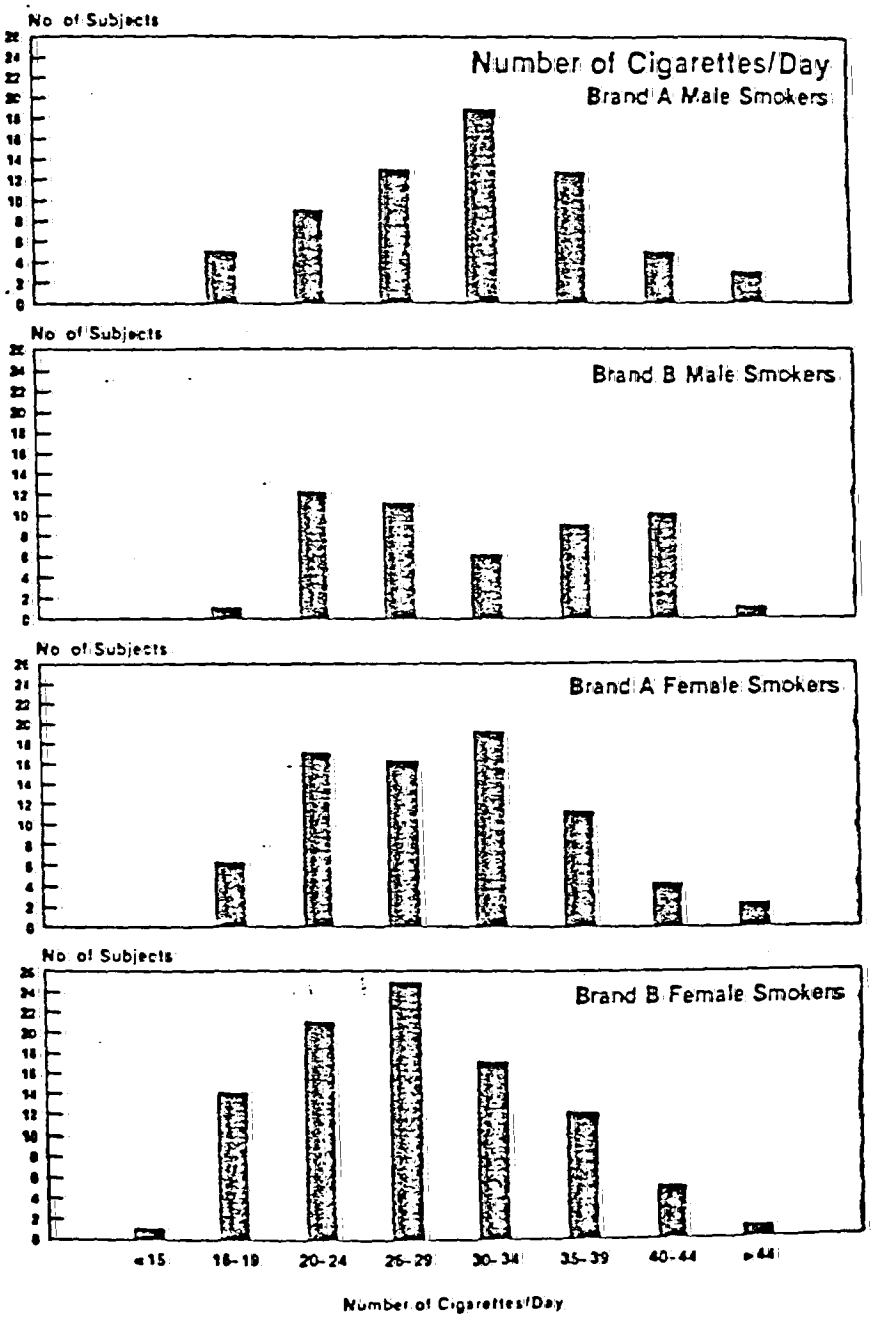
FIGURE 1



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Source: https://www.industrydocuments.ucsf.edu/docs/gzhl0000

FIGURE 2

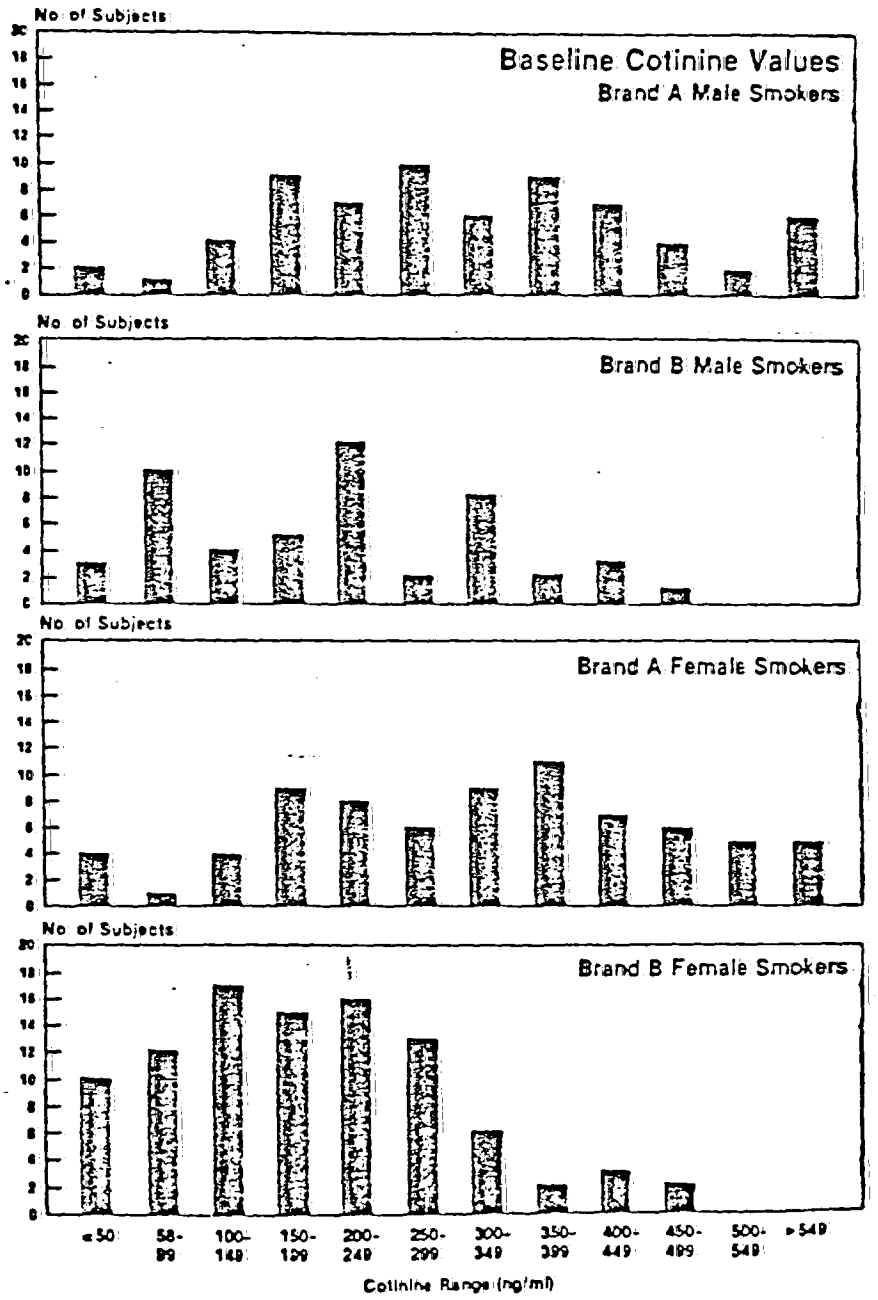

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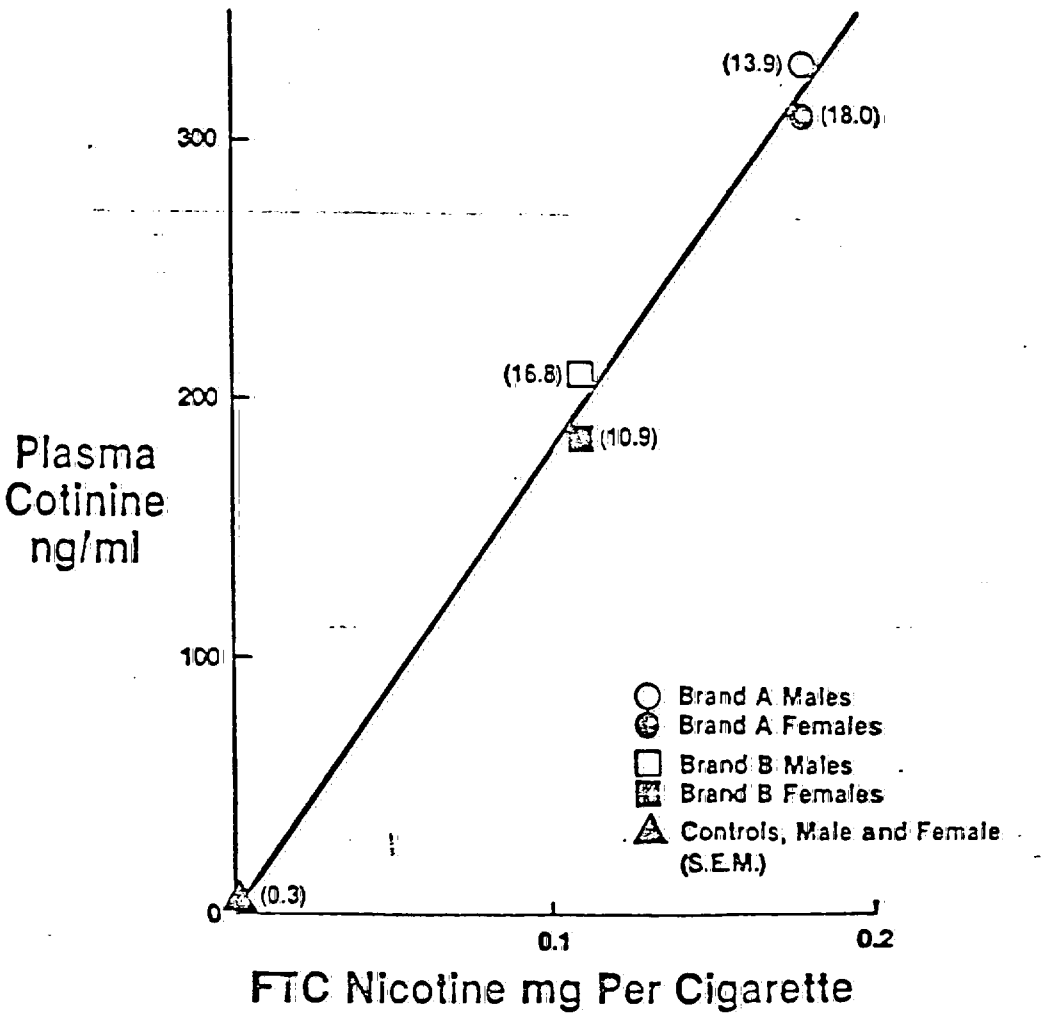
FIGURE 3



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Source: https://www.industrydocuments.ucsf.edu/docs/gzhl0000

FIGURE 4

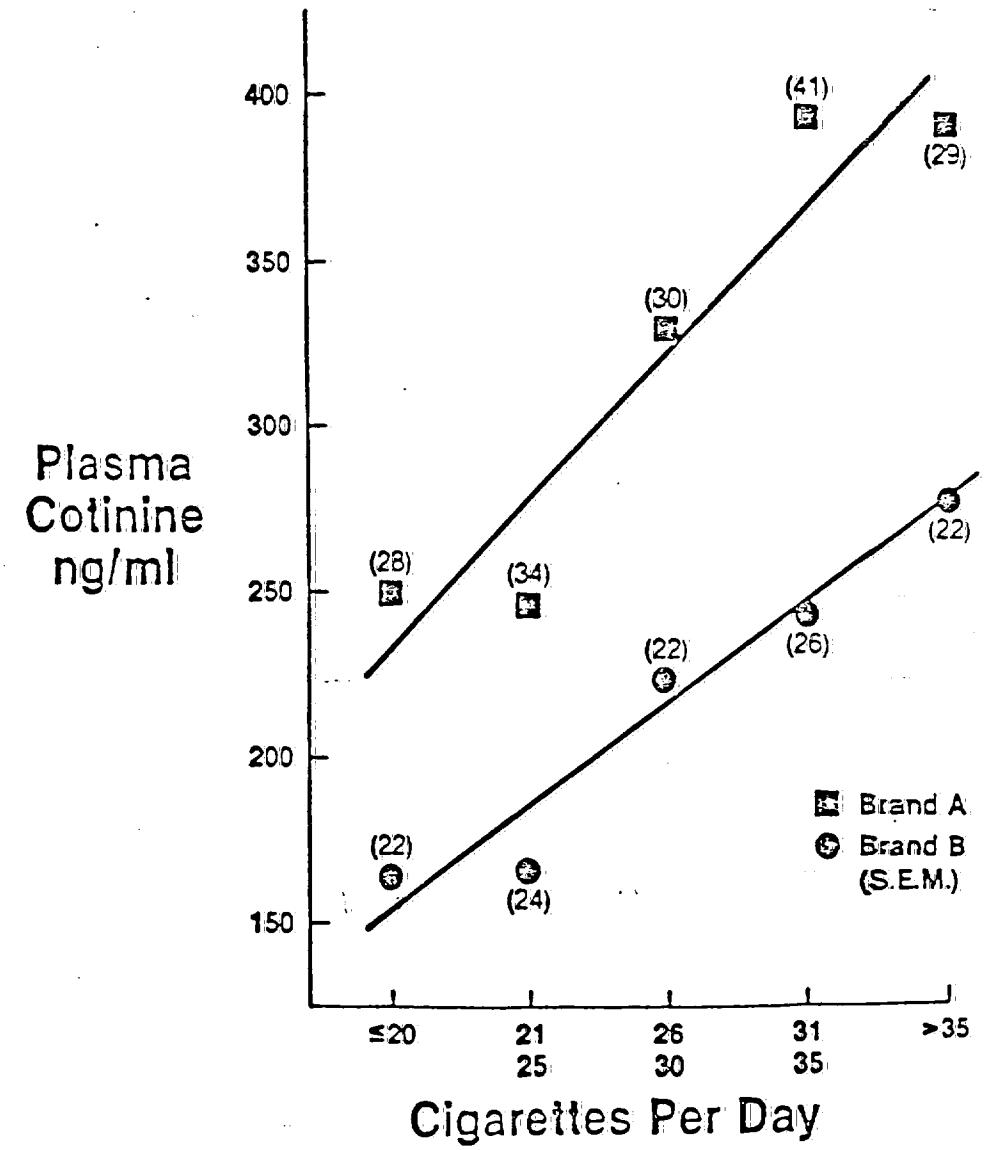

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FIGURE 5

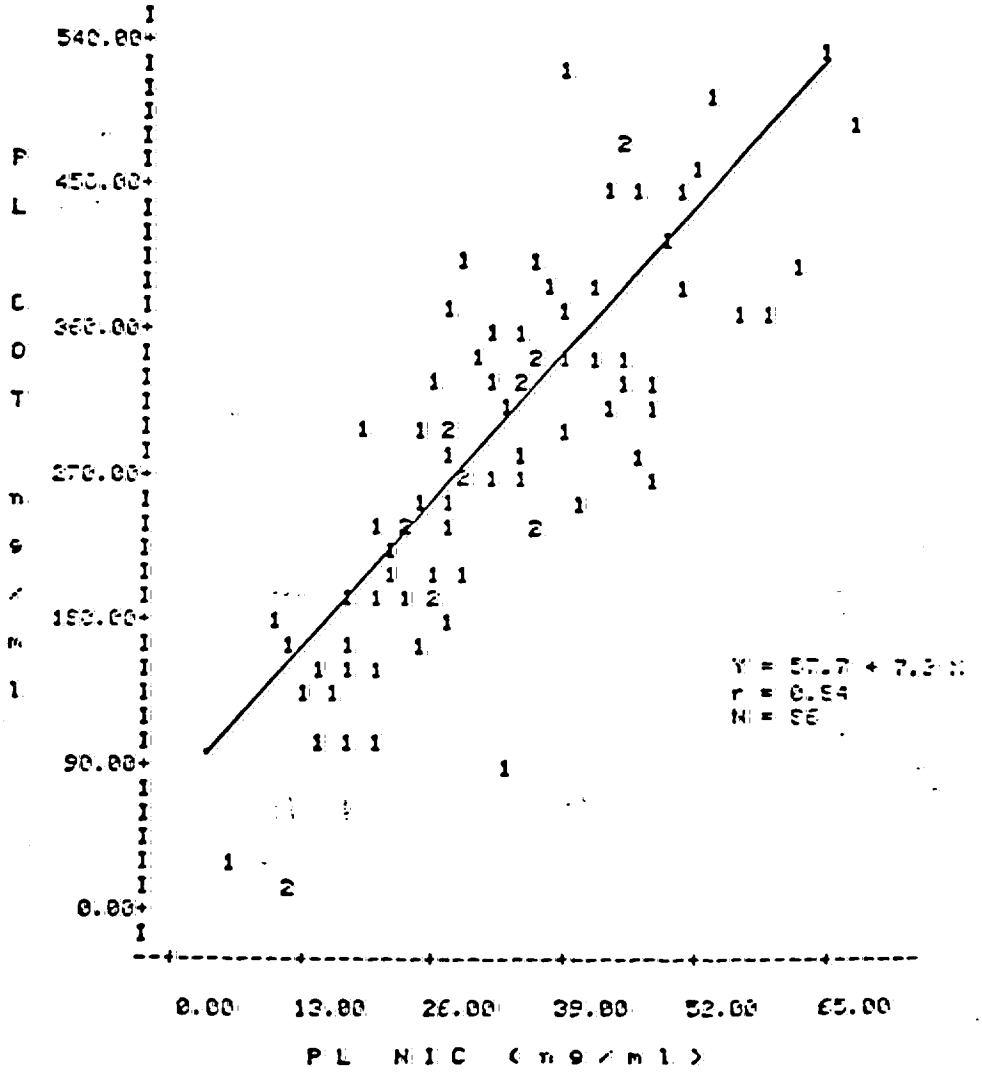

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FIGURE 6

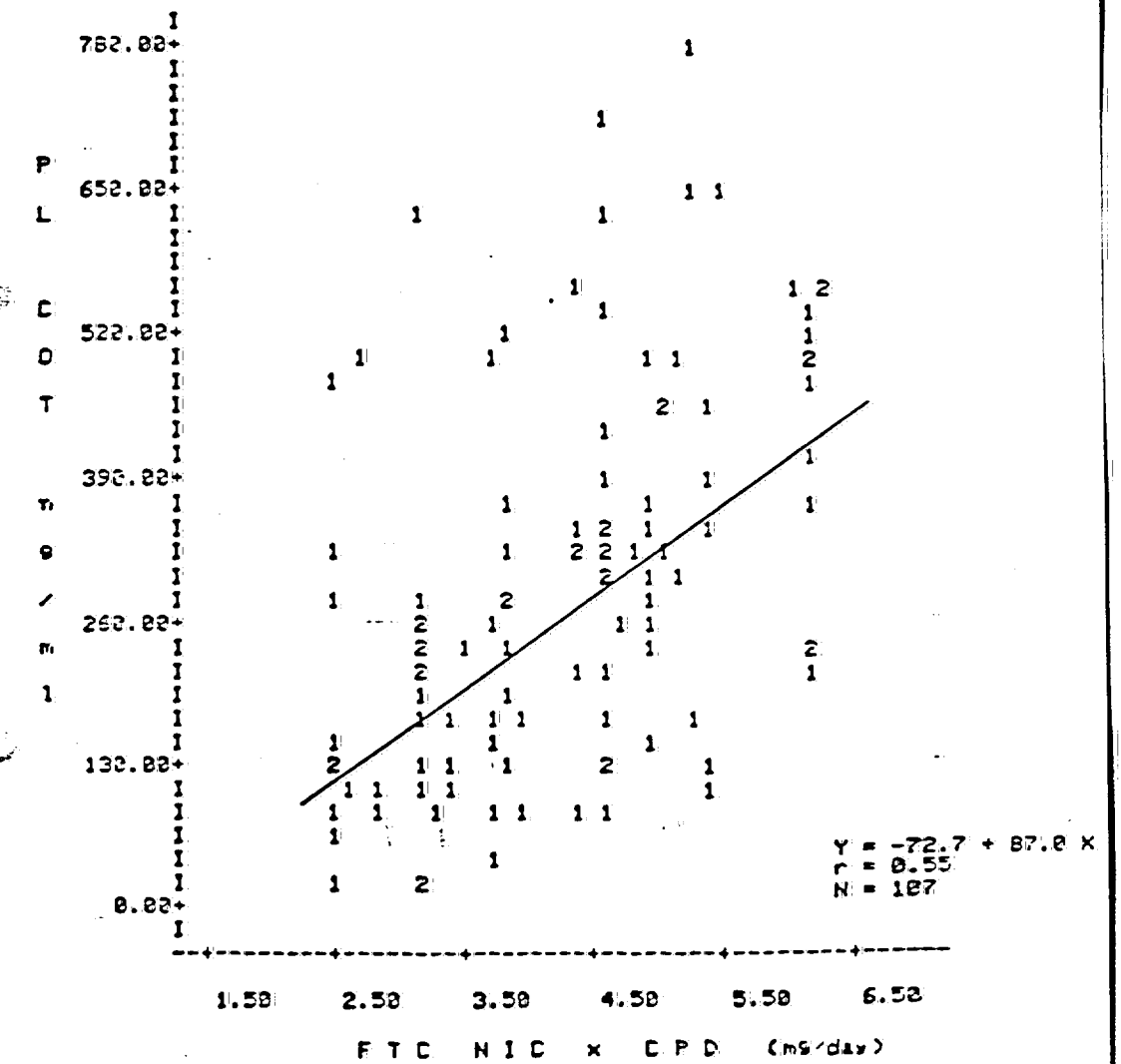

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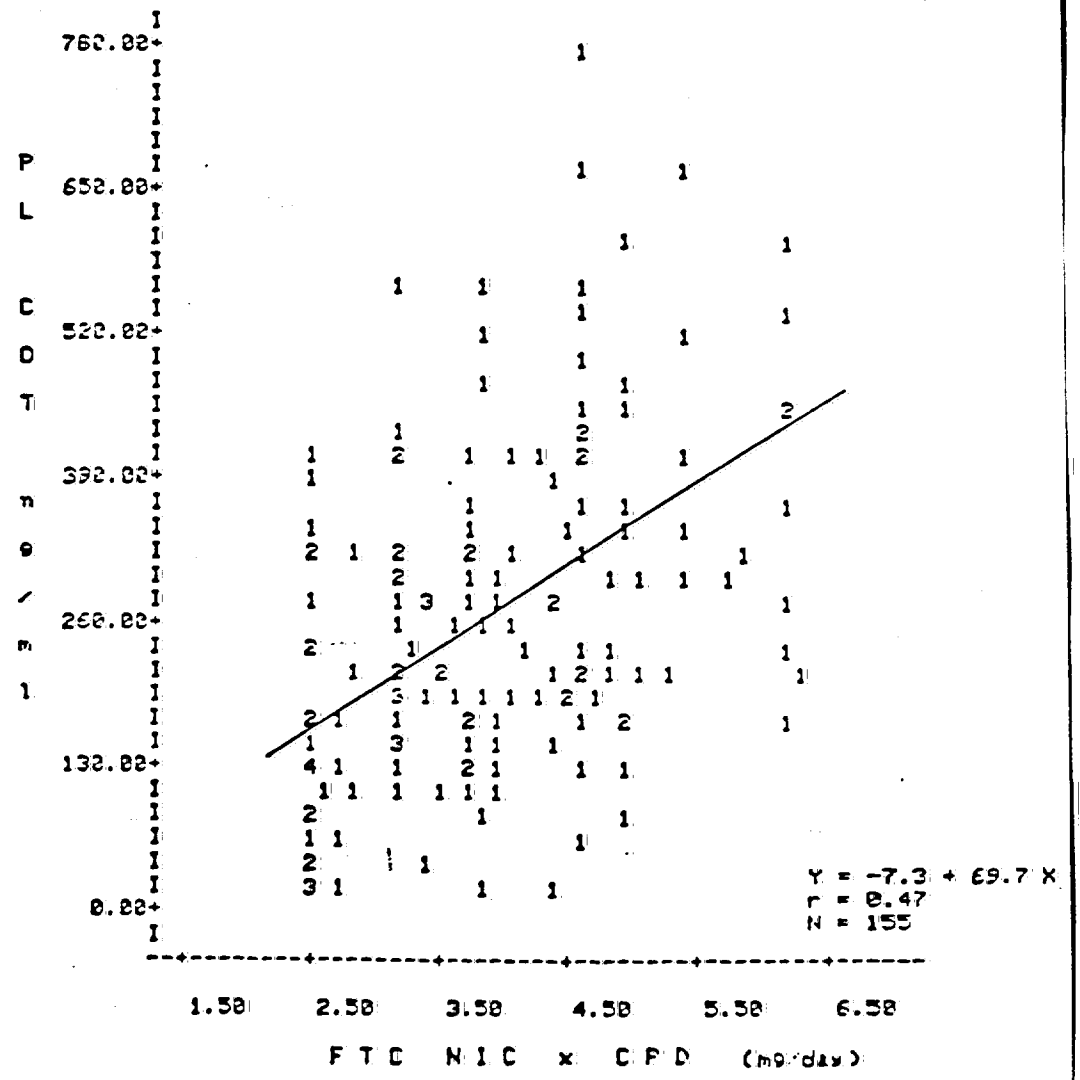
FIGURE 7



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Source: https://www.tobaccodocuments.ucsf.edu/docs/gzhl0000